IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Weaver *et al.*	Group Art Unit: Unassigned
Application No.: New Application	Examiner: Unassigned
Filed: August 15, 2001	
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Attorney Docket No.: NCI-006DV2	

Commissioner for Patents
Box Patent Application
Washington, D.C. 20231

CERTIFICATION UNDER 37 CFR 1.10

Date of Deposit: August 15, 2001 Mailing Label Number: EL 831 966 166 US

I hereby certify that paper or fee as enclosed are being deposited with the United States Postal Service on the date indicated above in an envelope as "Express Mail Post Office to Addressee" service under 37 C.F.R. §1.10 and addressed to Commissioner for Patents, BOX PATENT APPLICATION, Washington, D.C. 20231.

Larry Taylor
Name of Person Mailing Paper

Signature of Person Mailing Paper

PRELIMINARY AMENDMENT

Please amend the application as follows:

In the Specification:

At page 49, replace the paragraph starting at line 1 with the following paragraph:

β-Aryl-β-alanines were prepared in a one-pot reaction. In brief, to a solution of a substituted benzaldehyde in absolute ethanol was added malonic acid and excess ammonium

acetate, and the reaction mixture was heated to reflux. The reaction mixture was cooled to yield a mixture of the β-aryl-β-alanine and (in certain cases) a cinnamic acid derivative. The cinnamic acid (if present) was removed by acid/base extraction of the mixture to yield the β-aryl-β-alanine, often in moderate to good yield. The process is depicted in Figure 3, and further details of experimental procedures for the synthesis of certain β-aryl-β-alanine compounds are provided *infra*. A representative purification scheme for purifying the compounds is shown in Figure 4. Certain compounds prepared as described herein are set forth in Table 1, *infra*. Yield data are presented in two columns, the second being identical to that in Table 2, *infra*.

At page 50, replace Table 1 with the following Table:

Table 1. *β*-aryl-β-alanines prepared from benzaldehydes.

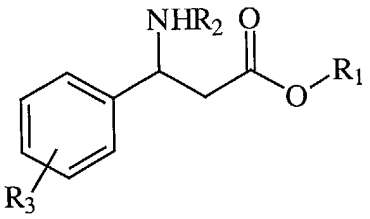
Compound $RCH(NH_2)CH_2COOH$ R =	Yield (%)	Yield (%) (from Table 2)
4-Fluorophenyl	68.5%	61.5%
4-Phenoxyphenyl	39.7%	68.1%
3-(4-methylphenoxy)phenyl	56.4%	56.4%
3-Methyl-4-methoxyphenyl	52.7%	52.7%
3-(3,4-dichlorophenoxy)phenyl	32.6%	42.6%
2-Methylphenyl	19.0%	19.0%
3-(4-chlorophenoxy)phenyl	23.2%	33.2%
2,5-Dimethyl-4-methoxyphenyl	12.6%	22.6%
4-Trifluoromethoxyphenyl	15.2%	46.2%
2-Chlorophenyl	21.7%	27.7%
2-Fluoro-3-trifluoromethylphenyl	5.5%	15.5%
3-Bromo-4-methoxyphenyl	23.8%	43.8%
4-Bromophenyl	34.2%	69.2%
Phenyl	61.1%	67.1%
4-Methylphenyl	51%	51.0%
4-Chlorophenyl	12%	65.0%
4-Acetamidophenyl	23%	23.0%
2,5-Dimethoxyphenyl	22%	22.0%
4-Diethylaminophenyl		
3-Methylphenyl	45.4%	45.8%
2-Hydroxy-3-methoxyphenyl	11%	17.2%
4-Phenylphenyl	40.2%	40.2%
3,4-Dibenzyloxyphenyl	36.2%	36.2%
3-[(3-Trifluoromethyl)phenyloxy]phenyl	29.7%	39.7%

At page 52, replace the paragraph starting at line 23 with the following paragraph:

Additional compounds as synthesized generally in accordance with the previous paragraphs, and analytical data therefor are provided below in Table 2.

Table 3.

A. Analytical and Biological Activity Data for β-Aryl-β-Alanines and Precursors

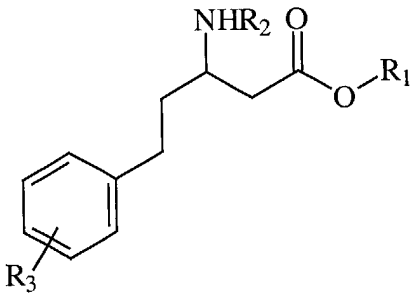


Compound	R_1	R_2	R_3	Yield[a] (%)	m.p. (°C)	TLC[b] (R_f)	IR (cm^{-1}) ν	H nmr[c] δ	Biological Activity[d]
B5P65	CH_3	Ac	H	97.4	58-61	0.42 (I)	3322 (NH), 1741 (C=O), 1649 (C=O)	[e]7.30 (m, 5H), 6.62 (br d, 1H, J=6.0 Hz), 5.43 (q, 1H, J=6.0 Hz), 3.62 (2, 3H), 2.89 (dd, 2H, J=5.9, 8.5 Hz), 2.02 (s, 3H)	NA
B6P140	CH_3	Ac	ρ-F_3C	87.1	Oil	0.52 (I)	3340 (NH), 1736 (C=O), 1654 (C=O)	[f]8.45 (d, 1H, J=8.0 Hz), 7.59 (d, 2H, J=8.3 Hz), 7.49 (d, 2H, J=8.1 Hz), 5.25 (q, 1H, J=7.6, 15 Hz), 3.55 (s, 3H), 2.75 (m, 2H), 1.82 (s, 3H)	NA
B5P91	H	H	H	61.1[g]	220-221	0.75 (I)	3305 (OH), 1627 (C=O)	[h]7.32 (s, 5H), 4.49 (t, 1H, J=7.9 Hz), 2.71 (d of t, 2H, J=6.5, 1.3 Hz)	0
B6P141	H	H·HCl	ρ-F_3C	93.0	203 (dec.)	0.60 (H)	3500-2900 (OH), 1715 (C=O)	[f]7.70 (d, 1H, J=8.1 Hz), 7.54 (d, 2H, J=8.1 Hz), 4.78 (dd, 1H, J=7.0, 7.3 Hz), 3.05 (m, 2H)	+1

a. EtOH, H_2O or a mix used for recrystallization; b. Solvent systems: I: EtOAc:MeOH 9:1; H: MeOH:AcOH 5:1; ^{1}H nmr solvents: e: $CDCl_3$, f: DMSO-*d6*, h: D_2O; Using pilocarpine, compound is active in rat at 100 mg/kg, or inactive; g. 48% [150].

Table 3 (continued).

B. Analytical and Biological Activity Data for β-Phenethyl-β-alanine and Precursors



Compound	R_1	R_2	R_3	Yield (%)	m.p. (°C)	TLC[b] (R_f)	IR (cm^{-1}) ν	H nmr[c] δ	Biological Activity[d]
B5P69	CH_3	Ac	ρ-CH_3O	93.8	Oil	0.54 (I)	3285 (NH), 1735 (C=O), 1651 (C=O)	[e]7.08 (d, 2H, J=8.5 Hz), 6.81 (d, 2H, J=8.7 Hz), 6.03 (br d, 1H, J=8.7 Hz), 4.27 (m, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 2.59 (t, 2H, J=8.2 Hz), 2.55 (d, 2H, J=8.4 Hz), 1.96 (s, 3H), 1.84 (q, 2H, J=8.2 Hz)	NA
B5P73	CH_3	Ac	H	98.6	Gum	0.68 (I)	3475 (NH), 1735 (C=O), 1654 (C=O)	[e]7.23 (m, 5H), 6.10 (br d, 1H, J=8.8 Hz), 4.30 (t of d, 1H, J=8.9, 5.4 Hz), 3.68 (s, 3H), 2.66 (t, 2H, J=8.2 Hz), 2.57 (dd, 2H, J=4.9, 3.0 Hz), 1.96 (s, 3H), 1.87 (m, 2H)	NA
B6P89	CH_3	Ac	ρ-CH_3	99.1	50-51	0.63 (I)	3288 (NH), 1731 (C=O), 1639 (C=O)	[e]7.07 (s, 4H), 6.08 (br d, 1H, J=8.8 Hz), 4.28 (sextet, 1H, J=5.3 Hz), 3.67 (s, 3H), 2.63 (d, 2H, J=8.2 Hz), 2.55 (m, 2H), 2.30 (s, 3H), 1.96 (s, 3H), 1.84 (quintet, 2H, J=7.9 Hz)	NA

Replace the entire page 61 with the following:

Table 3 (continued).

Compound	R_1	R_2	R_3	Yield[a] (%)	m.p. (°C)	TLC[b] (R_f)	IR (cm^{-1}) ν	H nmr[c] δ	Biological Activity[d]
B6P101	CH_3	Ac	*m*-NEt	100	Oil	0.62 (I)	3440 (NH), 1731 (C=O), 1653 (C=O)	[e]7.11 (t, 1H, J=7.5 Hz), 6.48 (br t, 3H), 6.05 (br d, 1H, J=8.4 Hz), 4.31 (m, 1H), 3.67 (s, 3H), 3.33 (q, 2H, J=7.0 Hz), 2.59 (t, 2H, J=8.4 Hz), 2.56 (d, 2H, J=4.4 Hz), 2.39 (br s, 1H), 1.94 (s, 3H), 1.87 (m, 2H), 1.14 (t, 3H, J=7.0 Hz)	NA
B6P113	CH_3	Ac	*m*,ρ-OCH_2O-	97.5	Oil	0.53 (I)	1729 (C=O), 1654 (C=O)	[e]7.01 (d, 1H, 8.4 Hz), 6.75 (d, 1H, J=8.4 Hz), 6.65 (m, 1H), 6.16 (m, 1H), 5.90 (s, 0.5H), 4.25 (m, 1H), 3.68 (s, 3H), 2.57 (m, 2H), 2.53 (m, 2H), 1.97 (s, 3H), 1.77 (m, 2H), 1.51 (impurity), 1.24 (impurity)	NA
B6P119	CH_3	Ac	ρ-OH *m*-CH_3O	60.0	Oil	0.80 (L)	3498 (OH), 1743 (C=O), 1663 (C=O)	[e]6.82 (d, 1H, J=7.9 Hz), 6.67 (m, 2H), 6.10 (br d, 1H, J=8.6 Hz), 5.56 (br s, 1H), 4.28 (m, 1H), 3.88 (s, 3H), 3.68 (s, 3H), 2.60 (d, 2H, J=8.4 Hz), 2.55 (t, 2H, J=2.2 Hz), 1.97 (s, 3H), 1.85 (m, 2H)	NA
B5P81	H	H	ρ-CH_3O	31.0	gum	0.34 (I), 0.70 (K)	3400-2500 (OH), 1632 (C=O)	[f]7.13 (d, 2H, J=8.6 Hz), 6.85 (d, 2H, J=8.5 Hz), 3.69 (s, 3H), 3.37 (m, 1H), 2.57 (t, 2H, J=8.0 Hz), 2.46 (m, 2H), 1.82 (m, 2H)	0

Replace the entire page 62 with the following:

Table 3 (continued).

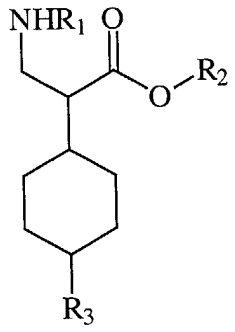
Compound	R_1	R_2	R_3	Yield[a] (%)	m.p. (°C)	TLC[b] (R_f)	IR (cm^{-1}) ν	H nmr[c] δ	Biological Activity[d]
B5P95	H	H	H	39.6	211-214[g]	0.37 (I)	3310 (OH), 1663 (C=O)	[k]8.36 (d, 5H, J=15.6 Hz), 4.92 (br s, 1H), 4.14 (br s, 2H), 3.95 (br d, 2H, J=8.0 Hz), 3.32 (br s, 2H)[i]	+1
B5P111	H	H	ρ-CH_3	66.9	206-207	0.89 (K)	3280 (OH), 1706 (C=O)	[k]8.20 (m, 4H), 4.89 (m, 1H), 4.10 (m, 2H), 3.87 (m, 2H), 3.38 (s, 3H), 3.28 (quintet, 2H, J=3.6 Hz)	Inactive
B6P145	H	H	ρ-OH *m*-CH_3O	98.4	oil	0.32 (I)	3447 (OH), 1718 (C=O)	[j]7.79 (br d, 1H, J=8.3 Hz), 6.68 (s, 1H), 6.65 (d, 1H, J=9.5 Hz), 6.49 (d, 1H, J=8.0 Hz) 4.00 (m, 1H), 3.69 (s, 3H), 2.43 (m, 2H), 2.30 (d, 2H, J=6.6 Hz), 1.76 (impurity), 1.63 (m, 2H)	+1

a. EtOH, H_2O or a mix used for recrystallization, where possible; b. Solvent systems: I: EtOAc:MeOH 9:1; L: EtOH:AcOH 50:1; K: MeOH:AcOH 5:1; c. ^1H nmr solvents: e: $CDCl_3$, f: D_2O, h: TFA-*d*, j: DMSO-*d6*; d. Using pilocarpine, compound is active in rat at 100 mg/kg, or inactive; g. 226-228°C (dec.)[194]; i. ^1H nmr in D_2O [144]..

Replace the entire page 63 with the following:

Table 3 (continued).

C. Analytical and Biological Activity Data for 4'-Substituted α-Cyclohexyl-β-alanine and Precursors



Compound	R_1	R_2	R_3	Yield[a] (%)	m.p. (°C)	TLC[b] (R_f)	IR (cm^{-1}) ν	H nmr[c] δ	Biological Activity[d]
B6P77	Ac	CH_3	H	93.5	Oil	0.80 (I)	1738 (C=O), 1674 (C=O)	[e]5.91 (br s, 1H), 4.14 (q, J=7.1 Hz)**, 3.69 (s, 3H), 3.53 (m, 1H), 3.32 (m, 1H), 2.46 (m, 1H), 1.94 (m, 5H), 1.26 (t, J=7.2 Hz)**, 1.14 (m, 6H)	NA
B6P81	Ac	CH_3	Ph	95.8	75-80	0.79 (L)	3259 (NH), 1730 (C=O), 1647 (C=O)	[e]7.29 (m, 5H), 7.19 (m, 2H), 5.94 (br s, 1H), 3.73 (s, 3H), 3.58 (m, 1H), 3.48 (m, 1H), 3.40 (m, 1H), 2.47 (m, 2H), 1.97 (s, 3H), 1.91 (m, 2H), 1.75 (m, 2H), 1.50 (m, 2H), 1.26 (m, 2H)	NA

Replace the entire page 64 with the following:

Table 3 (continued).

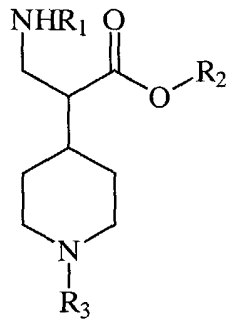
Compound	R_1	R_2	R_3	Yield[a] (%)	m.p. (°C)	TLC[b] (R_f)	IR (cm^{-1}) ν	H nmr[c] δ	Biological Activity[d]
B6P109	Ac	CH_3	$C(CH_3)_3$	98.3	73-75	0.70 (I)	3261 (NH), 1735 (C=O), 1648 (C=O)	[e]5.88 (br s, 1H), 3.69 (s, 3H), 3.53 (m, 1H), 3.41 (m, 1H), 3.34 (m, 1H), 2.44 (m, 1H), 1.94 (s, 3H), 1.77 (m, 2H), 1.63 (m, 1H), 1.50 (m, 1H), 1.27 (t, 1H, J=7.1 Hz), 1.00 (m, 4H), 0.82 (s, 9H)	NA
B5P107	H·HCl	H	Ph	33.5	268-270	0.74 (I)	3300-2500 (OH), 1701 (C=O)	[f]8.09 (br s, 0.5H), 7.18 (m, 5H), 3.29 (m, 1H), 3.01 (m, 1H), 2.87 (dd, 1H, J=4.0, 12.8 Hz), 2.57 (t, 1H, J=4.5 Hz), 2.45 (m, 1H), 1.75 (m, 5H), 1.29 (m, 3H)	+3
B5P119	H	H	H	51.9	238-240	0.75 (I)	3300-2700 (OH), 1635 (C=O)	[g]4.58 (quintet, 2H), 4.01 (m, 1H), 3.11 (m, 1H), 2.83 (m, 5H), 2.32 (m, 5H)	+1
B5P127	H·HCl	H	$C(CH_3)_3$	62.7	230 (dec)	0.91 (K)	3400-2700 (OH), 1732 (C=O)	[f]8.02 (br s, 3H), 2.97 (m, 1H), 2.84 (m, 2H), 2.51 (m, 1H), 1.71 (m, 3H), 1.63 (m, 2H), 0.95 (m, 4H), 0.79 (s, 9H)	0

** Partial Et-Me exchange has occurred due to solvolysis.

a. EtOH, H_2O or a mix used for recrystallizations; b. Solvent systems: I: EtOAc:MeOH 9:1; L: EtOH:AcOH 50:1; K: MeOH:AcOH 5:1; c. ^1H nmr solvents: e: $CDCl_3$, f: DMSO-*d6*, g. TFA-*d*, d. Using pilocarpine, compound is active in rat at 100 mg/kg, or inactive.

Table 3 (continued).

D. Analytical and Biological Activity Data for 4'-Substituted N-Acetyl-α-piperidinyl-β-alanine methyl ester



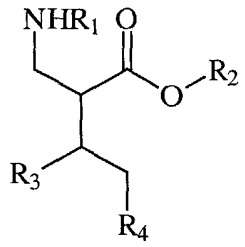
Compound	R_1	R_2	R_3	Yield (%)	m.p. (°C)	TLC[a] (R_f)	IR (cm^{-1}) ν	H nmr[c] δ	Biological Activity
B6P105	Ac	CH_3	CO_2Et	96.8	Gum	0.65 (I)	1743 (C=O), 1708 (C=O), 1673 (C=O)	5.92 (br s, 1H), 4.16 (q, J=6.6 Hz)**, 4.10 (q, 2H, H=7.1 Hz), 3.70 (s, 3H), 3.52 (m, 1H), 3.41 (m, 1H), 2.69 (m, 2H), 2.51 (m, 1H), 2.01 (m, 2H), 1.95 (s, 3H), 1.79 (m, 1H), 1.71 (d of m, 2H), 1.55 (d of m, 2H), 1.30 (t, J=6.6 Hz)**, 1.23 (t, 3H, J=7.0 Hz)	NA

** Partial Et-Me exchange has occurred due to solvolysis.

a. Solvent system: I: EtOAc:MeOH 9:1.

Table 3 (continued).

E. Analytical and Biological Activity Data for N-Acetyl-α-substituted-β-alanine methyl ester and α-Substituted-β-alanine



Compound	R_1	R_2	R_3	R_4	m.p. (°C)	Yield[a] (%)	TLC[b] (R_f)	IR (cm^{-1}) ν	H nmr (DMSO-*d6*) δ	Biological Activity[c]
B6P85	Ac	CH_3	$-CH_2CH_2CH_2-$		Oil	NA	0.54 (I)	1720 (C=O), 1660 (C=O)	7.78 (br s, 1H), 4.03 (q, J=7.0 Hz)**, 3.57 (s, 3H), 3.30 (m, 1H), 3.09 (m, 2H), 2.35 (m, 2H), 1.87 (m, 2H), 1.76 (s, 3H), 1.49 (m, 5H), 1.17 (t, J=7.0 Hz)**	NA
B6P93	Ac	CH_3	Et	CH_3	Oil	83.4	0.75 (I)	3189 (NH), 1723 (C=O), 1665 (C=O)	7.80 (br m, 1H), 3.58 (s, 3H), 3.26 (m, 1H), 3.04 (m, 1H), 2.59 (m, 1H), 1.76 (s, 3H), 1.5-1.1 (m, 5H), 0.9-0.7 (m, 6H)	NA

Replace the entire page 67 with the following:

Table 3 (continued).

Compound	R_1	R_2	R_3	R_4	m.p. (°C)	Yield[a] (%)	TLC[b] (R_f)	IR (cm^{-1}) ν	H nmr (DMSO-*d6*) δ	Biological Activity[c]
B6P97	Ac	CH_3	H	Bu	Gum	99.6	0.53 (I)	1739 (C=O), 1658 (C=O)	7.45 (br d, 1H, J=8.1 Hz), 3.70 (s, 3H), 2.51 (br d, 2H, J=6.3 Hz), 1.94 (s, 3H), 1.51 (br m, 2H), 1.33 (br m, 8H), 0.94 (m, 3H)	NA
B6P117	Ac	Et	$-CH_2(CH_2)_3CH_2-$		Oil	79.7	0.77 (I)	3216 (NH), 1727 (C=O), 1666 (C=O)	[d]5.89 (br s, 1H), 4.16 (d of q, 2H, J=7.0, 4.0 Hz), 3.62 (d of q, 1H, J=3.7, 13.5 Hz), 3.25 (d of q, 1H, J=5.2, 13.5 Hz), 2.52 (d of q, 1H, J=3.7, 9.5 Hz), 1.94 (s, 3H), 1.7-1.3 (br m, 11H), 1.27 (t, 3H, J=7.0 Hz)	NA
B6P133	Ac	Et	$-CH_2(CH_2)_8CH_2-$		Oil	98.5	0.75 (I)	3316 (NH), 1725)(C=O), 1661 (C=O)	7.88 (br s, 1H), 4.05 (q, 2H, J=8.1 Hz), 3.59 (m, 2H), 2.45 (m, 1H), 1.74 (s, 3H), 1.50 (m, 1H), 1.28 (m, 22H), 1.15 (t, 3H, J=8.1 Hz)	NA

Replace the entire page 68 with the following:

Table 3 (continued).

Compound	R_1	R_2	R_3	R_4	m.p. (°C)	Yield[a] (%)	TLC[b] (R_f)	IR (cm^{-1}) ν	H nmr (DMSO-*d6*) δ	Biological Activity[c]
B5P131	H·HCl	H	$-CH_2(CH_2)_8CH_2-$		201-204	36.7	0.79 (I)	3400-2700 (OH), 1722 (C=O)	12.72 (br s, 1H), 7.99 (br s, 3H), 2.98 (m, 1H), 2.82 (m, 1H), 2.68 (m, 1H), 1.91 (m, 1H), 1.28 (m, 24H)	Inactive

** Partial Et-Me exchange has occurred due to solvolysis.

a. Yield of last synthetic step; b. Solvent system: I: EtOAc:MeOH 9:1 c. Using pilocarpine, compound is active in rat at 100 mg/kg, or inactive; d. ^{1}H nmr solvent: $CDCl_3$.

At page 69, replace the paragraph starting at line 31 with the following paragraph:

The compounds of the invention listed in Tables 2 and 3, *supra*, were tested for biological activity per Example 6. The following compounds were found to have at least weak activity: β-p-methylphenyl-β-alanine hydrochloride, β-2-hydroxy-3-methoxyphenyl-β-alanine, β-3-methyl-4-methoxyphenyl-β-alanine (slight), β-3-(3,4-dichlorophenoxy)phenyl-β-alanine hydrochloride (moderate), β-2,5-dimethyl-4-methoxyphenyl-β-alanine, β-p-(trifluoromethoxy)phenyl-β-alanine, and β-2-fluoro-3-(trifluoromethyl)phenyl-β-alanine (moderate).

At page 70, replace the paragraph starting at line 22 with the following paragraph:

Example 6

Selected compounds were dissolved in 0.9% NaCl or suspended in a mixture of 30% polyethylene glycol 400 and 70% water, and tested in an animal model. Briefly, the compounds were administered intraperitoneally or or orally to carsworth Farms #1 mice (in a volume of 0.01 ml/g of body weight) or Sprague-Dawley rats (in a volume of 0.004 ml/g body weight). Times on peak effect and peak neurologic deficit were determined before the anticonvulsant tests were administered.

At page 71, replace the paragraph starting at line 11 with the following paragraph:

Example 7

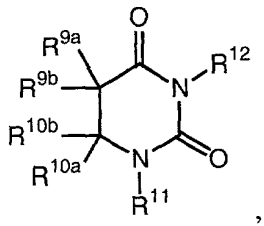
Testing of the dioxapiperazine compounds was performed in 12 mice at doses of 30, 100, 300 mg/kg (4 mice each) 30 minutes and four hours after the test compounds was administered. The results are shown in Table 4.

Pursuant to 37 CFR 1.121(b)(1)(iii), a marked up version of the amended text showing the changes made appears herein as Appendix A.

In the Claims:

Please cancel claim 1 without prejudice or disclaimer.
Please add the following claims:

68. (new) A method for inhibiting epileptogenesis, comprising administering to a subject in need thereof an effective amount of a compound represented by the formula:



, wherein

- R^{9a}, R^{9b}, R^{10a}, R^{10b} are each independently hydrogen, an alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, amino, hydroxy, thiol, alkylthiol, nitro, cyano, halogen, carboxyl, alkoxycarbonyloxy, aryloxycarbonyloxy, or aminocarbonyl group, or one of R^{9a} and R^{9b} and one of R^{10a} and R^{10b} are both taken together and form a double bond; or
- R^{9a} and R^{9b}, together with the two-carbon unit to which they are attached, are joined to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring;
- R^{10a} and R^{10b}, together with the two-carbon unit to which they are attached, are joined to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring; or one of R^{9a} and R^{9b} is joined with one of R^{10a} and R^{10b}, together with the two-carbon unit to which they are attached, to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring;
- R^{11} is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, or aryloxycarbonyl; or one of R^{10b} and R^{10b} is joined with R^{11}, together with the carbon atom and nitrogen atom to which

they are respectively attached, to form a heterocyclic ring having from 4 to 8 members in the ring; and

- R^{12} is selected from the group consisting of hydrogen, alkyl, aryl and a carbohydrate;

or a pharmaceutically acceptable salt thereof; such that epileptogenesis is inhibited.

69. (new) The method of inhibiting epileptogenesis according to claim 68 wherein

- R^{9a}, R^{9b}, R^{10a}, and R^{10b} are independently hydrogen or an alkyl, cycloalkyl, aryl, alkoxy, or aryloxy group; or one of R^{9a} and R^{9b} and one of R^{10a} and R^{10b} are both taken together and form a double bond; and
- R^{11} and R^{12} are each independently hydrogen, alkyl, or alkylcarbonyl.

70. (new) The method of inhibiting epileptogenesis according to claim 69 wherein R^{11} and R^{12} are hydrogen.

71. (new) The method of inhibiting epileptogenesis according to claim 69 wherein said R^{9a}, R^{9b}, R^{10a}, R^{10b}, R^{11}, or R^{12} alkyl or alkyloxy group has a straight or branched chain alkyl group having 20 or fewer carbon atoms in the backbone.

72. (new) The method of inhibiting epileptogenesis according to claim 71 wherein said alkyl group is substituted.

73. (new) The method of inhibiting epileptogenesis according to claim 72 wherein said alkyl group is substituted with an aryl group.

74. (new) The method of inhibiting epileptogenesis according to claim 69 wherein said R^{9a}, R^{9b}, R^{10a}, or R^{10b} cycloalkyl group has 4 to 10 carbon atoms in the ring structure.

75. (new) The method of inhibiting epileptogenesis according to claim 74 wherein said cycloalkyl group is substituted.

76. (new) The method of inhibiting epileptogenesis according to claim 75 wherein said cycloalkyl substituent is a *tert*-butyl or phenyl group.

77. (new) The method of inhibiting epileptogenesis according to claim 69 wherein said aryl group is substituted.

78. (new) The method of inhibiting epileptogenesis according to claim 73 wherein said aryl or said aryloxy group is substituted.

79. (new) The method of inhibiting epileptogenesis according to claim 77 wherein said aryl or aryloxy substitution is a halogen, hydroxyl, alkyl, alkoxyl, amino, aryloxy, alkyl amino, dialkylamino, arylamino, alkylcarbonylamino, or an aromatic moiety.

80. (new) The method of inhibiting epileptogenesis according to claim 78 wherein said aryl substitution is a halogen, hydroxyl, alkyl, alkoxyl, amino, aryloxy, alkyl amino, dialkylamino, arylamino, alkylcarbonylamino, or an aromatic moiety.

81. (new) The method of inhibiting epileptogenesis according to claim 79 wherein said aromatic moiety is a phenyl, naphthyl, quinolyl, or indolyl group.

82. (new) The method of inhibiting epileptogenesis according to claim 80 wherein said aromatic moiety is a phenyl, naphthyl, quinolyl, or indolyl group.

83. (new) The method of inhibiting epileptogenesis according to claim 81 wherein said phenyl group is substituted.

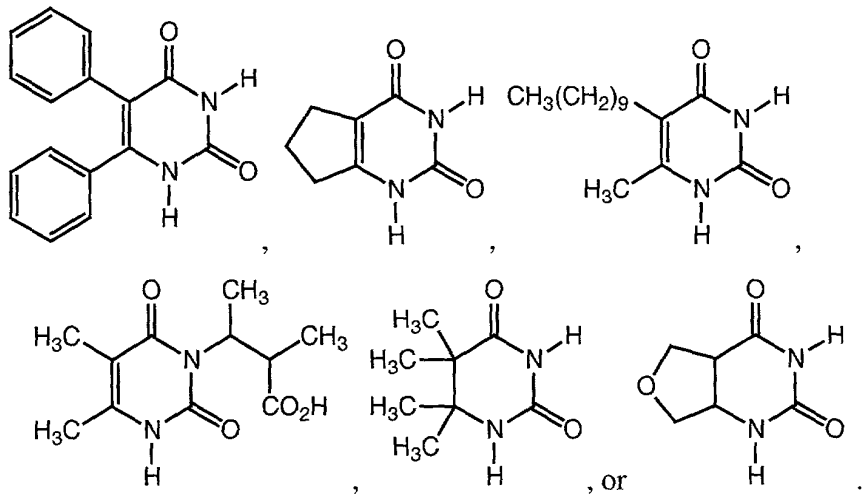
84. (new) The method of inhibiting epileptogenesis according to claim 82 wherein said phenyl group is substituted.

85. (new) The method of inhibiting epileptogenesis according to claim 83 wherein said substituted phenyl group is a 4-fluorophenyl, 4-phenoxyphenyl, 3-(4-methylphenoxy)phenyl, 3-methyl-4-methoxyphenyl, 3-(3,4-dichlorophenoxy)phenyl, 2-methylphenyl, 3-(4-chlorophenoxy)phenyl, 2,5-dimethyl-4-methoxyphenyl, 4-trifluoromethoxyphenyl, 2-chlorophenyl, 2-fluoro-3-trifluoromethylphenyl, 3-bromo-4-methoxyphenyl, 4-bromophenyl, 4-methylphenyl, 4-chlorophenyl, 4-acetamidophenyl, 2,5-dimethoxyphenyl, 4-diethylaminophenyl, 3-methylphenyl, 2-hydroxy-3-methoxyphenyl, 4-

phenylphenyl, 3,4-dibenzyloxyphenyl, or a 3-[(3-trifluoromethyl)phenyloxy]phenyl group.

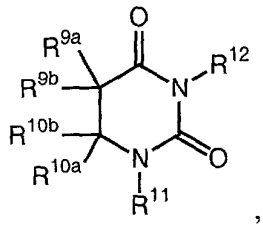
86. (new) The method of inhibiting epileptogenesis according to claim 84 wherein said substituted phenyl group is a 4-fluorophenyl, 4-phenoxyphenyl, 3-(4-methylphenoxy)phenyl, 3-methyl-4-methoxyphenyl, 3-(3,4-dichlorophenoxy)phenyl, 2-methylphenyl, 3-(4-chlorophenoxy)phenyl, 2,5-dimethyl-4-methoxyphenyl, 4-trifluoromethoxyphenyl, 2-chlorophenyl, 2-fluoro-3-trifluoromethylphenyl, 3-bromo-4-methoxyphenyl, 4-bromophenyl, 4-methylphenyl, 4-chlorophenyl, 4-acetamidophenyl, 2,5-dimethoxyphenyl, 4-diethylaminophenyl, 3-methylphenyl, 2-hydroxy-3-methoxyphenyl, 4-phenylphenyl, 3,4-dibenzyloxyphenyl, or a 3-[(3-trifluoromethyl)phenyloxy]phenyl group.

87. (new) A method of inhibiting epileptogenesis according to claim 68 wherein said compound is



, , , , , , or .

88. (new)A method for treating a convulsive disorder, comprising administering to a subject in need thereof an effective amount of a compound represented by the formula:



, wherein

- R^{9a}, R^{9b}, R^{10a}, R^{10b} are each independently hydrogen, an alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, amino, hydroxy, thiol, alkylthiol, nitro, cyano, halogen, carboxyl, alkoxycarbonyloxy, aryloxycarbonyloxy, or aminocarbonyl group, or one of R^{9a} and R^{9b} and one of R^{10a} and R^{10b} are both taken together and form a double bond; or
- R^{9a} and R^{9b}, together with the two-carbon unit to which they are attached, are joined to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring;
- R^{10a} and R^{10b}, together with the two-carbon unit to which they are attached, are joined to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring; or one of R^{9a} and R^{9b} is joined with one of R^{10a} and R^{10b}, together with the two-carbon unit to which they are attached, to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring;
- R^{11} is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, or aryloxycarbonyl; or one of R^{10b} and R^{10b} is joined with R^{11}, together with the carbon atom and nitrogen atom to which they are respectively attached, to form a heterocyclic ring having from 4 to 8 members in the ring; and
- R^{12} is selected from the group consisting of hydrogen, alkyl, aryl and a carbohydrate;

or a pharmaceutically acceptable salt thereof; such that said convulsive disorder is treated.

89. (new) The method of claim 88, wherein said compound is a substituted or unsubstituted uracil, dihydrouracil or β-ureidopropionate compound, or a derivative, analog, or a pharmaceutically acceptable salt thereof.

90. (new) The method of claim 89, wherein said uracil is a derivative selected from the group consisting of substituted pyrimidines, UMP and uridine, or analogs thereof.

Pursuant to 37 CFR 1.121(c)(1)(ii), a marked up version of the claims showing the changes made appears as Appendix B of this Response.

REMARKS

The present amendment is intended to correct certain clerical errors and to clarify certain presentations of data. This amendment is consistent with amendments entered in the parent case (US 09/041,371, filed March 11, 1998). Table 1 has been amended, for clarity, to also present the yield data from Table 2. The first appearance of "3-Methylphenyl" has been corrected for consistency with the corresponding entry in Table 2, page 55, second row (note that in original Table 1 this name appears twice) to the correct chemical name. Other clarifying text has also been included. Table 3 has been replaced with re-typed copies which are more suitable for reproduction. No new matter has been added.

Respectfully submitted,

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Dated: August 15, 2001

Appendix A: marked up versions of amendments to specification showing the changes made

At page 49, replace the paragraph starting at line 1 with the following paragraph:

β-Aryl-β-alanines were prepared in a one-pot reaction. In brief, to a solution of a substituted benzaldehyde in absolute ethanol was added malonic acid and excess ammonium acetate, and the reaction mixture was heated to reflux. The reaction mixture was cooled to yield a mixture of the β-aryl-β-alanine and (in certain cases) a cinnamic acid derivative. The cinnamic acid (if present) was removed by acid/base extraction of the mixture to yield the β-aryl-β-alanine, often in moderate to good yield. The process is depicted in Figure 3, and further details of experimental procedures for the synthesis of certain β-aryl-β-alanine compounds are provided *infra*. A representative purification scheme for purifying the compounds is shown in Figure 4. Certain compounds prepared as described herein are set forth in Table 1, *infra*. Yield data are presented in two columns, the second being identical to that in Table 2, *infra.*

At page 50, replace Table 1 with the following Table:

Table 1. β-aryl-β-alanines prepared from benzaldehydes.

Compound $RCH(NH_2)CH_2COOH$ R =	Yield (%)	Yield (%) (from Table 2)
4-Fluorophenyl	68.5%	61.5%
4-Phenoxyphenyl	39.7%	68.1%
3-(4-methylphenoxy)phenyl [3-Methylphenyl]	56.4%	56.4%
3-Methyl-4-methoxyphenyl	52.7%	52.7%
3-(3,4-dichlorophenoxy)phenyl	32.6%	42.6%
2-Methylphenyl	19.0%	19.0%
3-(4-chlorophenoxy)phenyl	23.2%	33.2%
2,5-Dimethyl-4-methoxyphenyl	12.6%	22.6%
4-Trifluoromethoxyphenyl	15.2%	46.2%
2-Chlorophenyl	21.7%	27.7%
2-Fluoro-3-trifluoromethylphenyl	5.5%	15.5%
3-Bromo-4-methoxyphenyl	23.8%	43.8%
4-Bromophenyl	34.2%	69.2%
Phenyl	61.1%	67.1%
4-Methylphenyl	51%	51.0%
4-Chlorophenyl	12%	65.0%
4-Acetamidophenyl	23%	23.0%
2,5-Dimethoxyphenyl	22%	22.0%
4-Diethylaminophenyl		
3-Methylphenyl	45.4%	45.8%
2-Hydroxy-3-methoxyphenyl	11%	17.2%
4-Phenylphenyl	40.2%	40.2%
3,4-Dibenzyloxyphenyl	36.2%	36.2%
3-[(3-Trifluoromethyl)phenyloxy]phenyl	29.7%	39.7%

At page 52, replace the paragraph starting at line 23 with the following paragraph:

Additional compounds as synthesized generally in accordance with the previous paragraphs, and analytical data therefor are provided below in Table 2.

At page 69, replace the paragraph starting at line 31 with the following paragraph:

The compounds of the invention listed in Tables 2 and 3, *supra*, were tested for biological activity per Example 6. The following compounds were found to have at least weak activity: β-p-methylphenyl-β-alanine hydrochloride, β-2-hydroxy-3-methoxyphenyl-β-alanine, β-3-methyl-4-methoxyphenyl-β-alanine (slight), β-3-(3,4-dichlorophenoxy)phenyl-β-alanine hydrochloride (moderate), β-2,5-dimethyl-4-methoxyphenyl-β-alanine, β-p-(trifluoromethoxy)phenyl-β-alanine, and β-2-fluoro-3-(trifluoromethyl)phenyl-β-alanine (moderate).

At page 70, replace the paragraph starting at line 22 with the following paragraph:

Example 6

Selected compounds were dissolved in 0.9% NaCl or suspended in a mixture of 30% polyethylene glycol 400 and 70% water, and tested in an animal model. Briefly, the compounds were administered intraperitoneally or or orally to carsworth Farms #1 mice (in a volume of 0.01 ml/g of body weight) or Sprague-Dawley rats (in a volume of 0.004 ml/g body weight). Times on peak effect and peak neurologic deficit were determined before the anticonvulsant tests were administered.

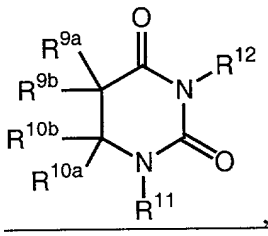
At page 71, replace the paragraph starting at line 11 with the following paragraph:

Example 7

Testing of the dioxapiperazine compounds was performed in 12 mice at doses of 30, 100, 300 mg/kg (4 mice each) 30 minutes and four hours after the test compounds was administered. The results are shown in Table 4.

Appendix B: marked up version of the claims showing the changes made

68. (new) A method for inhibiting epileptogenesis, comprising administering to a subject in need thereof an effective amount of a compound represented by the formula:



, wherein

- R^{9a}, R^{9b}, R^{10a}, R^{10b} are each independently hydrogen, an alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, amino, hydroxy, thiol, alkylthiol, nitro, cyano, halogen, carboxyl, alkoxycarbonyloxy, aryloxycarbonyloxy, or aminocarbonyl group, or one of R^{9a} and R^{9b} and one of R^{10a} and R^{10b} are both taken together and form a double bond; or
- R^{9a} and R^{9b}, together with the two-carbon unit to which they are attached, are joined to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring;
- R^{10a} and R^{10b}, together with the two-carbon unit to which they are attached, are joined to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring; or one of R^{9a} and R^{9b} is joined with one of R^{10a} and R^{10b}, together with the two-carbon unit to which they are attached, to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring;
- R^{11} is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, or aryloxycarbonyl; or one of R^{10b} and R^{10b} is joined with R^{11}, together with the carbon atom and nitrogen atom to which they are respectively attached, to form a heterocyclic ring having from 4 to 8 members in the ring; and

- R^{12} is selected from the group consisting of hydrogen, alkyl, aryl and a carbohydrate;

or a pharmaceutically acceptable salt thereof; such that epileptogenesis is inhibited.

69. (new) The method of inhibiting epileptogenesis according to claim 1 wherein

- R^{9a}, R^{9b}, R^{10a}, and R^{10b} are independently hydrogen or an alkyl, cycloalkyl, aryl, alkoxy, or aryloxy group; or one of R^{9a} and R^{9b} and one of R^{10a} and R^{10b} are both taken together and form a double bond; and
- R^{11} and R^{12} are each independently hydrogen, alkyl, or alkylcarbonyl.

70. (new) The method of inhibiting epileptogenesis according to claim 2 wherein R^{11} and R^{12} are hydrogen.

71. (new) The method of inhibiting epileptogenesis according to claim 2 wherein said R^{9a}, R^{9b}, R^{10a}, R^{10b}, R^{11}, or R^{12} alkyl or alkyloxy group has a straight or branched chain alkyl group having 20 or fewer carbon atoms in the backbone.

72. (new) The method of inhibiting epileptogenesis according to claim 4 wherein said alkyl group is substituted.

73. (new) The method of inhibiting epileptogenesis according to claim 5 wherein said alkyl group is substituted with an aryl group.

74. (new) The method of inhibiting epileptogenesis according to claim 2 wherein said R^{9a}, R^{9b}, R^{10a}, or R^{10b} cycloalkyl group has 4 to 10 carbon atoms in the ring structure.

75. (new) The method of inhibiting epileptogenesis according to claim 7 wherein said cycloalkyl group is substituted.

76. (new) The method of inhibiting epileptogenesis according to claim 8 wherein said cycloalkyl substituent is a *tert*-butyl or phenyl group.

77. (new) The method of inhibiting epileptogenesis according to claim 2 wherein said aryl or said aryloxy group is substituted.

78. (new) The method of inhibiting epileptogenesis according to claim 6 wherein said aryl group is substituted.

79. (new) The method of inhibiting epileptogenesis according to claim 10 wherein said aryl or aryloxy substitution is a halogen, hydroxyl, alkyl, alkoxyl, amino, aryloxy, alkyl amino, dialkylamino, arylamino, alkylcarbonylamino, or an aromatic moiety.

80. (new) The method of inhibiting epileptogenesis according to claim 11 wherein said aryl substitution is a halogen, hydroxyl, alkyl, alkoxyl, amino, aryloxy, alkyl amino, dialkylamino, arylamino, alkylcarbonylamino, or an aromatic moiety.

81. (new) The method of inhibiting epileptogenesis according to claim 12 wherein said aromatic moiety is a phenyl, naphthyl, quinolyl, or indolyl group.

82. (new) The method of inhibiting epileptogenesis according to claim 13 wherein said aromatic moiety is a phenyl, naphthyl, quinolyl, or indolyl group.

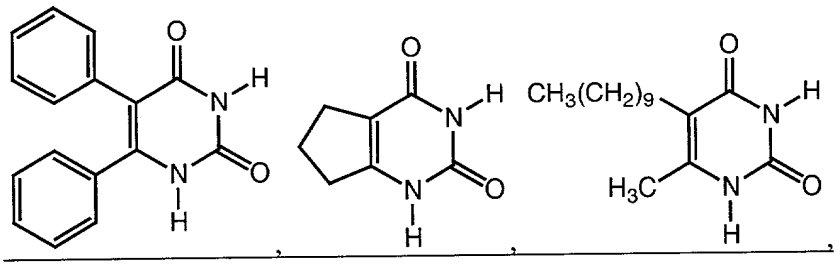
83. (new) The method of inhibiting epileptogenesis according to claim 14 wherein said phenyl group is substituted.

84. (new) The method of inhibiting epileptogenesis according to claim 15 wherein said phenyl group is substituted.

85. (new) The method of inhibiting epileptogenesis according to claim 16 wherein said substituted phenyl group is a 4-fluorophenyl, 4-phenoxyphenyl, 3-(4-methylphenoxy)phenyl, 3-methyl-4-methoxyphenyl, 3-(3,4-dichlorophenoxy)phenyl, 2-methylphenyl, 3-(4-chlorophenoxy)phenyl, 2,5-dimethyl-4-methoxyphenyl, 4-trifluoromethoxyphenyl, 2-chlorophenyl, 2-fluoro-3-trifluoromethylphenyl, 3-bromo-4-methoxyphenyl, 4-bromophenyl, 4-methylphenyl, 4-chlorophenyl, 4-acetamidophenyl, 2,5-dimethoxyphenyl, 4-diethylaminophenyl, 3-methylphenyl, 2-hydroxy-3-methoxyphenyl, 4-phenylphenyl, 3,4-dibenzyloxyphenyl, or a 3-[(3-trifluoromethyl)phenyloxy]phenyl group.

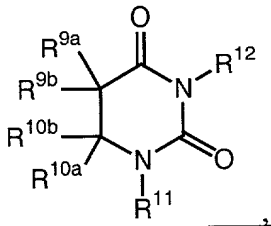
86. (new) The method of inhibiting epileptogenesis according to claim 17 wherein said substituted phenyl group is a 4-fluorophenyl, 4-phenoxyphenyl, 3-(4-methylphenoxy)phenyl, 3-methyl-4-methoxyphenyl, 3-(3,4-dichlorophenoxy)phenyl, 2-methylphenyl, 3-(4-chlorophenoxy)phenyl, 2,5-dimethyl-4-methoxyphenyl, 4-trifluoromethoxyphenyl, 2-chlorophenyl, 2-fluoro-3-trifluoromethylphenyl, 3-bromo-4-methoxyphenyl, 4-bromophenyl, 4-methylphenyl, 4-chlorophenyl, 4-acetamidophenyl, 2,5-dimethoxyphenyl, 4-diethylaminophenyl, 3-methylphenyl, 2-hydroxy-3-methoxyphenyl, 4-phenylphenyl, 3,4-dibenzyloxyphenyl, or a 3-[(3-trifluoromethyl)phenyloxy]phenyl group.

87. (new) A method of inhibiting epileptogenesis according to claim 1 wherein said compound is



, , , , , , or .

88. (new)A method for treating a convulsive disorder, comprising administering to a subject in need thereof an effective amount of a compound represented by the formula:



, wherein

- R^{9a}, R^{9b}, R^{10a}, R^{10b} are each independently hydrogen, an alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aryloxycarbonyl, amino, hydroxy, thiol, alkylthiol, nitro, cyano, halogen, carboxyl, alkoxycarbonyloxy, aryloxycarbonyloxy, or aminocarbonyl group, or one of R^{9a} and R^{9b} and one of R^{10a} and R^{10b} are both taken together and form a double bond; or
- R^{9a} and R^{9b}, together with the two-carbon unit to which they are attached, are joined to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring;
- R^{10a} and R^{10b}, together with the two-carbon unit to which they are attached, are joined to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring; or one of R^{9a} and R^{9b} is joined with one of R^{10a} and R^{10b}, together with the two-carbon unit to which they are attached, to form a carbocyclic or heterocyclic ring having from 4 to 8 members in the ring;
- R^{11} is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, or aryloxycarbonyl; or one of R^{10b} and R^{10b} is joined with R^{11}, together with the carbon atom and nitrogen atom to which they are respectively attached, to form a heterocyclic ring having from 4 to 8 members in the ring; and
- R^{12} is selected from the group consisting of hydrogen, alkyl, aryl and a carbohydrate;

or a pharmaceutically acceptable salt thereof; such that said convulsive disorder is treated.

89. (new) The method of claim 21, wherein said compound is a substituted or unsubstituted uracil, dihydrouracil or β-ureidopropionate compound, or a derivative, analog, or a pharmaceutically acceptable salt thereof.

90. (new) The method of claim 22, wherein said uracil is a derivative selected from the group consisting of substituted pyrimidines, UMP and uridine, or analogs thereof.